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THE EFFECT OF CHLORALHYDRATE UPON THE
PROPERTIES OF HEART-MUSCLE.

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[FROM THE PHYSIOLOGICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY.]

Dissertation submitted to the Board of University Studies of the Johns
Hopkins University in conformity with the requirements
for the degree of Doctor of Philosophy

BALTIMORE

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PREFACE

The thesis that it is desired to maintain within this paper is, that the normal vertebrate heart shows a well defined period during which the muscle can not be excited to contraction or made to yield extra systoles, and that this period of inexcitability is limited to the early part of systole. This period, within the accompanying paper, has been called the *absolute refractory period*.

Only a part of the results of the investigation of the problem has been set forth in this paper. It, however, embodies essentially the same conclusions that have been arrived at as a result of a large number of other experiments. In these experiments the heart was treated with varying percentages of potassium chloride, calcium chloride, carbon dioxide, chlorine water, and several anesthetics, and the effect of very strong induction shocks was studied with a view to shortening the *absolute refractory period*. On account of the importance ascribed to the action of chloralhydrate upon the heart, it was thought best to publish separately the results contained in this article.

The main body of facts accumulated since the publication of this paper is now in manuscript and will be published at an early date.



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THE EFFECT OF CHLORALHYDRATE UPON THE PROPERTIES OF HEART-MUSCLE.

By W. H. SCHULTZ.

[From the Physiological Laboratory of the Johns Hopkins University.]

RECENTLY there appeared in the "Archiv für experimentelle Pathologie und Pharmakologie" an article by Rohde¹ in which he discusses the effect of chloralhydrate upon the heart of the frog. His conclusions may be given as follows:

1. The refractory period, during early stages of the poisoning, is shortened without any change in the threshold value of the stimulus. In more advanced stages of poisoning the refractory period is apparently abolished.

2. The all or none law ceases to hold.

3. Summation may occur in early stages of the poisoning at a time when the contractile energy of the muscle has in no wise been impaired.

4. With gradually advancing stages of poisoning, the heart, in response to stimuli of a low frequency, yields compound contractions resembling incomplete tetanus, and finally yields a true summated tetanus.

5. Through the agency of chloralhydrate the intrinsic nerve centres of the heart are paralyzed before the fibres are. This is the equivalent of anatomically removing the otherwise inseparable centres of the apex so that under these conditions the heart-muscle acts as a strip of intestinal muscle or as a *Limulus* heart deprived of its centres.

In view of the significance of these conclusions, should they prove correct, I have repeated Rohde's experiments with results such as will be set forth in this paper.

¹ ROHDE: Archiv für experimentelle Pathologie und Pharmakologie, 1905, lxiv, p. 104.

METHOD.

Three series of experiments were carried on, the first of which included experiments upon the heart, *in situ*, of *Pseudemys elegans* and *P. rugosa* and upon ventricular strips taken from the same species. The second series included experiments upon the heart of *Rana hylecina*, and the third series upon the heart of large specimens of *Rana catesbiana*.

In the second and third series of experiments the skin was clipped just above the occipital condyles and a narrow-bladed scalpel thrust into the slight depression immediately back of the tip of the parasphenoid until the medulla was reached. Then by carefully inserting a bent ligating needle into the incision and passing it first forward and then backward, the brain and anterior portion of the spinal cord were destroyed with scarcely any loss of blood. The animal was then securely pinned, dorsal side downward, to a flat piece of cork, — the skin, muscle, and sternum severed by a longitudinal incision and spread apart so as to expose the heart. Then the heart was clamped in the region of the auriculo-ventricular junction by means of a Gaskell clamp, yet not firmly enough to cut off the blood from the ventricle. Into the apex of the ventricle was inserted a fine platinum hook which was fastened by means of a thread to one end of a straw-recording lever directly above the heart. This hook also functioned as one of the electrodes. The other electrode was a fine needle so placed that its point could be brought into contact with any portion of the ventricle without materially injuring the surface of the heart or interfering with its movement. Single break shocks from an induction coil were used, the primary coil being supplied by a current from one or two large Edison-Lalande cells. The threshold stimulus was determined as soon as the specimen was in place, and its relative strength was expressed by the distance in centimetres between the primary and secondary coils.¹ Except when testing the absolute refractory period² this strength of stimulus was used until a change in the irritability of the heart was noticed, whereupon the strength of the stimulus was increased or decreased so as to insure the use of a stimulus slightly above the threshold. It was necessary to exercise this precaution inasmuch as the hearts of different frogs, and indeed of each individual frog, may vary in irritability.

¹ For convenience the strength of stimulus will be spoken of as 51 cm., etc.

² Absolute refractory period corresponds to the time of systole.

Two sets of records were taken in each experiment. The first set included a series taken before the injection as soon as possible after the heart was exposed, whereas the second set included records taken under like conditions except that from time to time measured quantities of chloralhydrate solution were injected into the anterior abdominal vein. This was done with a syringe which could be refilled and manipulated without interfering with the heart, the contractions of which were being recorded without intermission except during the few minutes required to change the kymograph paper.

The moment of stimulation was recorded upon the myogram by means of a spark¹ from an induction coil. This method insures great accuracy, and one is thus enabled to determine in what phase of the contraction the stimulus becomes effective.

RESULTS.

In dosing the heart with chloralhydrate (0.75 per cent), it was found that so large an injection as 4-6 c.c. usually resulted fatally, and that under these conditions successive stages of poisoning followed each other so quickly as to render the study of them difficult. On the whole, the dose which proved most satisfactory for initial injections was 2 c.c., after which doses of such size were administered as would keep the heart under the influence of the drug.

The first effect noticed after the injection of 2 c.c. of chloralhydrate was a marked decrease in the height of the contraction, accompanied either by a partial or temporary loss of rhythmicity. If a like dose were repeated before the heart had to any considerable extent recuperated, the added depression was likely to prove fatal, as was the case with too large an initial dose. However, if sufficient time elapsed between the first and second injections, recovery set in, and the height of the diminished contraction gradually approximated that of the normal contraction. During early stages of the experiment notable changes in the heart phenomena were evident,—the refractory period was shortened, the heart responding during any part of the diastolic phase to such stimuli as were used in determining the original threshold stimulus; appropriate stimuli usually

¹ This method is a modification of the one described by E. A. SCHÄFER in the *Internationale Monatschrift für Anatomie und Physiologie*, 1888, v, p. 152. See Fig. 1 for diagram illustrating the principal parts of the key devised for sending in break shocks and recording the moment of stimulation simultaneously. A detailed description of this key will be published later.

became effective at a time corresponding to late systole; the heart upon the application of successive stimuli yielded compound contractions resembling summation and tetanus; the irritability gradually increased to a given maximum, after which it steadily decreased as the poisoning advanced; the power to contract automatically was more or less impaired and the heart on the whole showed a decreased rate of contraction.

During later stages of the poisoning the heart grew more and more sluggish; the phenomena of so-called summation and tetanus became more prominent; the power of the ventricle to yield automatic contractions was lost; as the contractility diminished stronger induction shocks had to be administered in order to call forth extra contractions during a given diastole; and finally the muscle ceased to respond even to very strong shocks.

REFRACTORY PERIOD.

It is well known that electrical stimuli administered during the systolic phase of the normal heart are ineffective, and that a weak stimulus sent in during late diastole which calls forth an extra systole might fail to do so if applied to the heart during early diastole. It would seem, therefore, that the refractory period may be limited to the time of systole plus a portion of diastole. By applying appropriate stimuli the portion extending into diastole may be shortened. This portion of the refractory period is for convenience designated as the *variable refractory period*, whereas that portion corresponding to the time of systole and which towards electrical stimuli remains constant, is called the *absolute refractory period*. To illustrate, in Fig. 2, *a*, dots 4, 6, . . . 24 represent effective stimuli, and 2 represents an ineffective stimulus. In the first contraction the last non-refractory point lies somewhere between *c* and *d*, this point being called *x*. The variable refractory period, then, corresponds to the portion of the cardiac cycle represented by *abx*. In Fig. 2, *b*, it will be seen that stimuli 4, 8, 10, 12, 14, 16, and 22 are within the absolute refractory period; stimuli 18 and 20 at the end of systole mark the termination of the absolute refractory period, the latter period extending, as above stated, from the beginning of the systolic phase to the last non-refractory point therein. Hence stimuli 4 and 22 of this figure fall within the absolute refractory period, whereas 6 falls within the variable refractory period.

From an example analogous to Rohde's Fig. 1, *a, b*, p. 107, it can be seen that the early shortening of the refractory period described

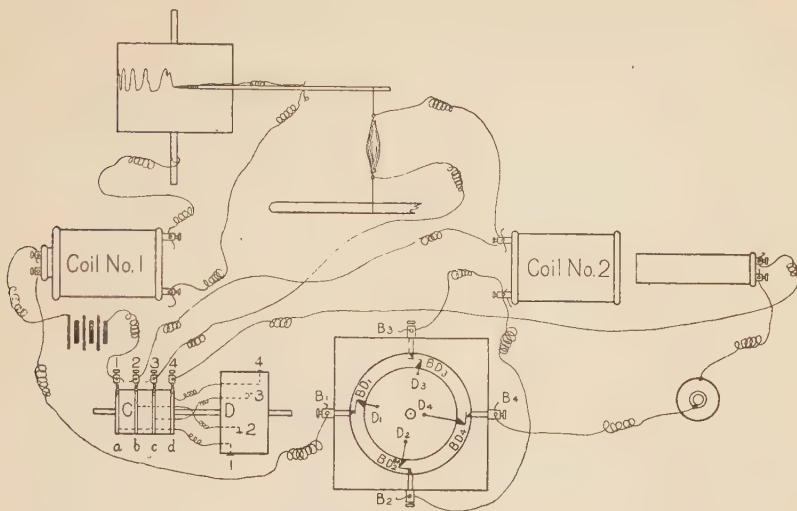


FIGURE 1.— To show the arrangement for recording the moment of stimulation on the cardiogram. By means of a special key a break induction shock is sent into the heart from coil 2 at the same instant as an induction current from a large Rhumkorff coil (coil 1) is sent through the recording lever. The key is composed of two principal parts, *B* and *D*, and *C*. *B* and *D* consists of two parts, the drum *D* with four contacts, *D* 1, 2, 3, and 4; the brush holder with four copper brushes joined to binding posts, *B* 1, 2, 3, and 4 respectively. A cross section of *B* and *D* is shown by the lower right hand figure which not only illustrates the arrangement of the contacts and brushes, but also the method of connecting the contacts to the wires which lead to the bands of the commutator *C*. This commutator forms the second part of the key, serving to continue the circuit which may be closed in the revolution of the drum by any one of the contacts *D* 1, 2, 3, or 4 respectively. This is accomplished by these four copper brushes being connected with binding posts 1, 2, 3, and 4 and being in contact with bands *a*, *b*, *c*, and *d* respectively. Coil 1 generates the spark used in recording the moment of stimulation when the circuit of its primary is broken at *BD*₁. Coil 2 generates the induction shock used as a stimulus when the circuit to its primary is broken at *BD*₄, the circuits at *BD*₄ and *BD*₁ being broken simultaneously. In order to rule out the make shocks of coil No. 2, the secondary coil is short-circuited at *BD*₂. After the make shock has been short-circuited, contact *BD*₂ is broken and the muscle is thrown into the circuit of the secondary of coil 2 by making contact *BD*₃. After this if the drum be rotated so as to break contacts *BD*₁ and *BD*₄, the muscle is stimulated at the same time that a spark generated by coil 1 knocks off a bit of soot from the record, thus recording the moment of stimulation.

by him involves only the variable refractory period. Let it be supposed that the atropinized heart yielded contractions like those in Fig. 2, *b*, and that such a heart, though responding to a stimulus in

the diastolic phase at point 32, failed to do so at point 31. After treating the heart with chloralhydrate it responded not only to stimuli 31 and 32, but also to a stimulus of equal strength that was applied at the beginning of the diastolic phase. One effect, therefore, of the chloral poisoning was to shorten the refractory period. The first non-refractory point having been moved from between points 31 and 32 to the end of the systole, it is clear that only the variable refractory period was shortened. As is known, this variable refractory period can be shortened either by increasing the strength of the

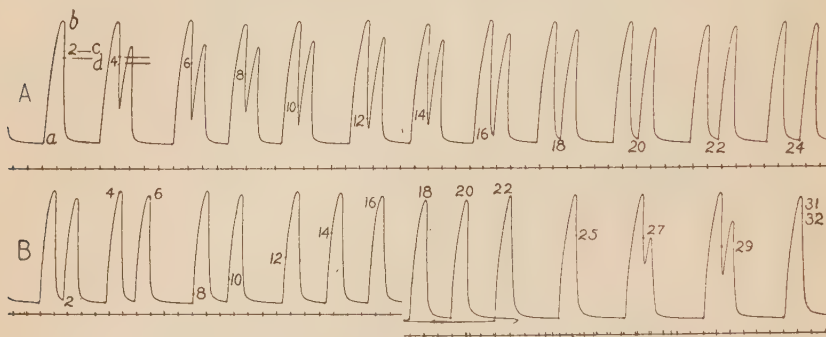


FIGURE 2. — About one-half the original size. *A* and *B* taken from a ventricular strip (*P. elegans*) *A*. — *a b x*, (*x* being the last non-refractory point between *c* and *d*) of the first contraction represents the variable refractory period; points 4, 6, . . . 24 represent effective stimuli in the period of diastole. *B*. — The absolute refractory period corresponds to the time of systole, included between points 18 and 20. Points 4, 8, . . . 16 and 22 are in the absolute refractory period; stimuli 6, 25, 31, and 32 are in the variable refractory period.

stimulus or by increasing the irritability of the heart. My experiments,¹ unlike Rohde's,² indicate that an increased irritability accompanies the shortening of the variable refractory period. It is reasonable to suppose that this irritability is a result of the changed condition of the muscle, which in turn causes a shortening of the variable refractory period.

Fig. 3, *f*, is a tracing of Rohde's Fig. 2, *b*. It will be noticed that for the third contraction the fourth to seventh stimuli inclusive fall within the time of systole, and that this contraction is greater in extent than the first, second, and fourth contractions. This increased height

¹ See record of experiments, p. 498.

² ROHDE: "Doch habe ich vielfach feststellen können, dass der Schwellenwert der wirksamen Reize in keiner Phase der Chloralvergiftung absinkt." *Loc. cit.*, p. 108.

in the contraction Rohde attributes to the combined action of the aforementioned stimuli. Likewise Rohde leads one to infer that for the fifth contraction, the tenth to thirteenth stimuli inclusive, each acting in its turn, result in a heightened systole like that described for the third contraction. In addition to the apparent action of these successive

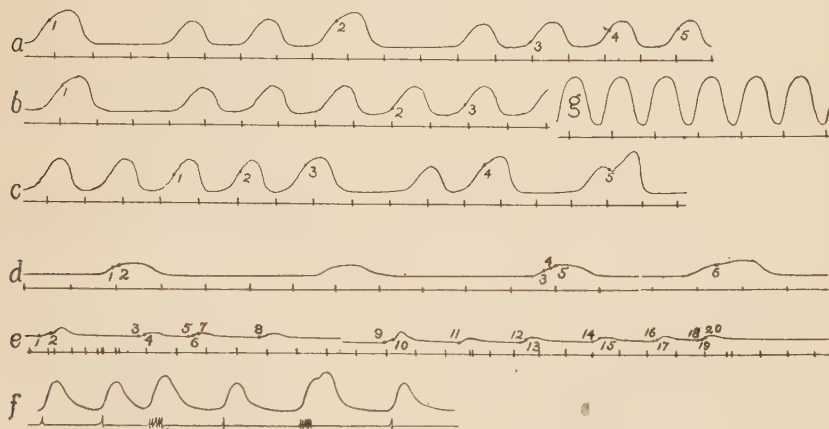


FIGURE 3. — About two-thirds the original size. *a*, *b*, *c*, thirty-four minutes after first intravenous injection. 10 c.c. of 0.75 per cent chloralhydrate solution having been injected in doses of 2 c.c. each. Threshold stimulus S23 cm. Strength used in these records S21 cm. Stimuli *a* 1 and 2, *b* 1, and *c* 3, falling in late systole result in increased extent of contraction. Stimuli *c* 4 and 5 and *d* 6 show this phenomenon to be due to added contractions. Stimuli *b* 2 and 3, *c* 1 and 2, *d* 1 and 2, *d* 3, 4, and 5, *e* 4, and *e* 6 and 7 are each ineffective and show the presence of an absolute refractory period. *d*, same heart ninety-one min. after first injection; 14 c.c. injected; threshold stimulus S21 cm.; stimulus used S18 cm. *e*, same as *d*, only later stage of poisoning; threshold stimulus S19 cm.; stimulus used S18 cm. *f*, tracing of Rohde's figure 2 *b*, p. 108. *g*, contractions from undrugged heart used later for *a*, *b*, *c*, *d*, and *e*.

stimuli, stimulus 14 instead of simply augmenting the already increased extent of the contraction, is followed by an extra contraction. If all of the above stimuli are effective, as above stated, such a condition would lead to the conclusion that the absolute refractory period had entirely disappeared, or that the absolute refractory period was masked by the successive contractions of separate parts of the muscle, the stimuli which were apparently effective during systole being in reality only effective for those parts in diastole. That is, the base of the ventricle, because of the slow propagation of the contraction wave, was passing into diastole at a time at which the apex was in systole. An extra stimulus for the base would therefore be effective,

and the new systole would either augment the extent of the contraction or would result in an extra summated contraction, depending upon the manner in which the new contraction wave overlapped the previous wave.

Fig. 3, *a b c*, represents a heart in about the same stage of poisoning as that represented by Fig. 3, *f*. The heart following stimuli 1 and 2 of *a*, 1 of *b*, and 3 of *c*, especially the latter, responds with contractions of increased height. Contraction 5, *c*, is analogous to the third contraction of Fig. 3, *f*, and contractions 1 and 2, *a*, and 1, *b*, illustrate the same phenomena. It will also be noticed that in Fig. 3, *a*, contractions 6, 7, and 8 show a gradual rise which may be due to stimuli 3, 4, and 5, but in Fig. 3, *b*, contractions 2, 3, and 4 following a compensatory pause show a similar increase in height, whereas in Fig. 3, *c*, contractions 1, 2, 3, and 4 do not follow a pause, yet show no difference in height, although stimuli 1 and 2 fall in the period of systole at a time corresponding to stimuli 4 and 5 respectively of Fig. 3, *a*. This would seem to indicate, therefore, that stimuli 3, 4, and 5 of Fig. 3, *a*, are ineffective, and that the increase in height is due to *trappe*. Furthermore, the evidence that stimuli are ineffective during the earlier part of the period of systole is to be found in such a record as 3, *d*. The heart was not stimulated during the second contraction, but in the first, third, and fourth contractions, stimuli 1 and 2, 3, 4 and 5, and 6 were applied to the heart during its period of systole, as represented by contractions 1, 3, and 4 respectively. Stimulus 6, during the time of late systole, was effective, but stimuli 1 and 2, 3, 4 and 5 at an earlier period of systole were ineffective. It would seem, therefore, from these experiments, that in Fig. 3, *f*, copied from Rohde, it is not stimuli 4, 5, and 6 of the third contraction, and stimuli 10, 11, and 12 of the fifth contraction, but stimuli 7 and 13 which cause the increase in the extent of contractions 3 and 5 respectively. Therefore the absolute refractory period, though shortened, is still present, and corresponds at this stage of the poisoning to the greater part of the systolic period.

Thus far I have laid particular stress upon the fact that the shortening of the absolute refractory period and the degree of poisoning seem to bear no definite ratio to each other and that after the first sudden shortening of the absolute refractory period it extends over a certain definite portion of the systole despite the gradual loss in contractility. Let us now consider the more advanced stages of poisoning at a time at which the force of the contraction has been greatly reduced.

Fig. 4, *a*, illustrates records of normal contractions, and *b* records from the same heart seven minutes after injecting something over 2 c.c. of the solution. It will be noticed that in the case of the simple contractions 5 and 6, the extra stimulus during systole was ineffective. In the compound contraction 7, the extra stimulus has fallen in the shortened absolute refractory period.

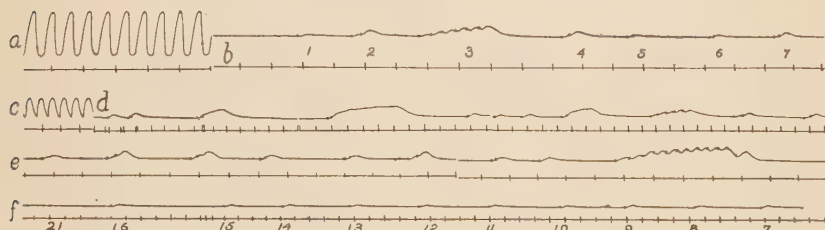


FIGURE 4.—About four-sevenths the original size. *a*, *Rana catesbiana* (medium size) undrugged heart. *b*, 7 min. after intravenous injection of 2-4 c.c. of 0.75 per cent chloralhydrate; stimulus, S13 cm. *c*, *R. catesbiana*, undrugged heart. *d*, same as *c* 10-15 min. after intravenous injection of 5 c.c. of solution. *e*, Last stages of poisoning, *f*, very late stage of poisoning, illustrating All or None Law. In contractions *b*, 5 and 6, *e*, 4, 5 and 6, the second stimulus of each is ineffective. In contractions *b*, 4 and 7, *d*, 11, and *e*, 3, the second is an added contraction. Contractions *d*, 3, 4, and 8 due to fibrillary twitches called forth in each case by a single strong stimulus.

In Fig. 4, *e*, owing to the long latent period and the slowness of the contraction, it was possible to exercise a greater range of choice as to the moment of stimulation than in Fig. 4, *b*. The absolute refractory period is shortened as shown in the second and third contractions, yet there is a definite refractory period that remains even at this very late stage of poisoning. (See contractions 4, 5, and 7, Fig. 4, *e*.)

Fig. 4, *c*, *d*, illustrates another phase of poisoning. The records were taken from a heart that was very irritable, and early in the course of the experiment, before the first injection, showed a marked decrease in the force of its contractions. There was then injected from 4 to 5 c.c. of chloralhydrate solution with the result that the heart soon ceased to yield spontaneous contractions. Record *d*, contractions 3, 4, and 8 show extra contractions in response to stimuli late in the systole. By reason of the magnification used, the lever moved so rapidly that it was impossible to exercise much choice as to the moment of sending in an extra stimulus during the short systole. The extra response, furthermore, was made up of fibrillary twitches which, when viewed through a hand lens, seemed to be limited to the region

of the electrodes. These few twitches resulted in a kind of contraction, so that in this case there apparently was no absolute refractory period. However, I can confirm Rohde's statement to the effect that, "Bei starkeren graden der Vergiftung ist die refraktäre Period anscheinend ganz verschwunden," if particular emphasis be laid on his proviso, "anscheinend."

While in certain cases it may appear that the heart responds to single induction shocks in any part of the extremely short systole, yet by reason of the small amount of muscle which is brought into play in producing such a small contraction, it is just as probable that the second stimulus calls into action fibres which were but slightly affected by the first stimulus. In this case there would still be present an absolute refractory period which, however, would be masked by the contraction of a different set of fibres in response to the second stimulus, the effect of this stimulus being recorded during the systole of the first set.

In spite of the evidence in my experiments, which favors the idea that the refractory period persists as long as the contractility, let us grant that it may disappear at a time when the contraction is so faint as to make it practically impossible to prove its presence, of what significance would it be in support of the neurogenic theory? If, as Rohde maintains, chloralhydrate affects the nervous mechanism before it does the muscle, and the refractory period depends for its existence upon the intrinsic ganglia, then we ought to expect it to disappear with rhythmicity or at least long before the contractility. I have proven conclusively that the refractory period persists at least until the muscle has lost its rhythmicity, and with the exception of a slight shortening remains intact until the contractions are so faint that it is impossible to experiment successfully during the systolic phase. As I shall try to show later, it is not necessary to adopt Rohde's assumption in order to explain the effect of chloralhydrate.

THE ALL OR NONE LAW.

In the chloralized heart, as in the normal heart, an increase in the strength of the stimulus is not accompanied by an increase in the extent of the contraction. Preparations in various stages of poisoning were tested, yet in no instance was it possible to confirm satisfactorily Rohde's statement to the effect that the all or none law is done away with. Variations in the height of the contractions were met with,

but these seemed to be due to *treppe*. The same may be said regarding such a phenomenon as is illustrated by Rohde's Fig. 5, p. 111, in which the extra systole resulting from an artificial stimulus during the time of late diastole was higher than the preceding spontaneous contractions. This increase in the extent of the extra contraction is commonly met with in the normal heart, and can be easily explained as the effect of *treppe*.

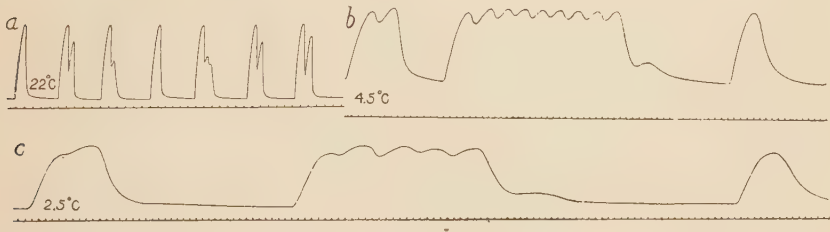


FIGURE 5.— About one-fourth the original size. *a*, *b*, and *c* show records taken from a strip of ventricular muscle (*P. elegans*), which was first immersed in a solution of 0.7 per cent sodium chloride and 0.025 per cent calcium chloride. When the solution was drawn off, the muscle was stimulated while in a moist chamber, the air of which was cooled. (*a*)—taken at 22° C.; (*b*), at 4.5° C.; (*c*), at 2.5° C. Contractions 1 *b* and 1 *c* simulate summation of skeletal muscle; contractions 2 *b* and 2 *c* simulate incomplete tetanus of skeletal muscle.

In Fig. 4, *f*, a tracing is given which shows that at a very late stage of the poisoning, increase in the strength of the stimulus does not result in an increase in the extent of the contraction.

I am unable to reconcile the difference in the results as indicated by Fig. 4, *f*, and Rohde's Fig. 4, p. 110, this figure appearing the same as mine except that an increase in the strength of the stimulus is followed by an increase in the height of the contraction. In conclusion, I can only say that my data lead me to conclude that the all or none law prevails in hearts drugged with chloralhydrate.

SUMMATION.

At an early stage of chloralhydrate poisoning of the frog's heart, it is possible to secure a compound contraction from two successive stimuli, such as is represented in Fig. 3, *c* (Fig. 1, *b*, Rohde). At the proper stage of poisoning the compound contraction thus obtained may give a curve resembling in all respects one from a summated contraction of skeletal muscle. Similar results may be obtained also from excised strips of the terrapin's ventricle after immersion in a

solution of chloralhydrate. As is well known, such a phenomenon cannot be obtained from normal heart-muscle under the usual conditions of temperature. So far as the effect of chloralhydrate is concerned Rohde states that this summation may be obtained at a stage of poisoning during which the force of contraction from a given stimulus shows no decrease in extent. In my experiments, on the contrary, it was found in all cases that the action of the chloralhydrate had caused a decrease in the extent of the individual contractions before the phenomenon of summation was obtainable. A suggestive fact observed in this connection was that in some cases strips which had been immersed in a solution of chloralhydrate and which were exhibiting the phenomenon of summation displayed a difference in contractility at the two ends. A mechanical stimulus applied at one end gave a weaker contraction than when applied at the other end. So also in the case of the drugged frog's heart a similar difference might be observed between the base and the apex of the ventricle. It seems possible, therefore, that the apparent summation following upon successive stimuli may be due to added contractions of separate parts—that is, the excitation wave aroused by the first stimulus may involve only a part of the muscle, while the second stimulus following at the end of the refractory period of the first contraction may excite the formerly quiescent part and thus give an apparent summation. Such a result, as is well known, may be obtained from a strip of ventricular muscle in which a partial block has been established by compression or by section. A similar result was obtained in a series of experiments made upon strips of ventricular muscle from the terrapin which were immersed in a solution containing 0.7 per cent of sodium chloride and 0.025 per cent of calcium chloride and which were kept at a temperature between 0° and 1° C. When such a preparation in a moist chamber and at a temperature of 1° C. is stimulated, it responds with contractions which show not only a slow systole and diastole, but are also of smaller extent than at room temperatures. If now a preparation of this kind is given two successive stimuli so timed that the second stimulus falls at the beginning of the diastole of the first contraction, a summated or compound contraction results which resembles closely, as is shown by Fig. 5, contractions *b* 1 and *c* 1, the curves obtained at an advanced stage of chloral poisoning. It is most probable that lowering the temperature to this extent depresses the metabolic processes in the heart, and possibly in this case also the wave of excitation from the first stimulus fails to involve

the whole of the muscular strip. Whether or not this suggestion is correct, the parallelism between the action of the low temperature and the poisoning by chloralhydrate is significant. The evidence would indicate that the ability to give a summated contraction is connected in some way with a slowing and weakening of the normal metabolic processes within the muscle itself.

TETANUS.

If the normal heart be stimulated during the time of early diastole by single break shocks such as will call forth an extra systole, and

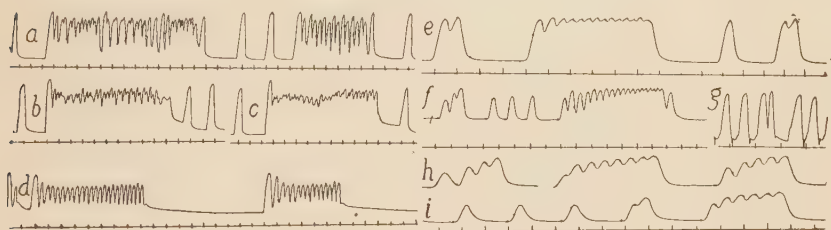


FIGURE 6. — About four-ninths the original size. *a, b, c, d, e* records taken from same heart. *a*, undrugged, showing effect of successive stimuli. *b* and *c* show effect of rapid tetanic stimuli. *d*, heart short time after an intravenous injection. *e*, about forty minutes after injecting something over 3 c.c. of solution. *f, g, h, i, j* records from another heart. *f, g*, later stage of poisoning than that represented by *e, g*, normal heart showing relative diminution in extent of contraction as compared with compound contraction of drugged heart. *h* and *i*, later stage of poisoning than *f*.

this process be repeated a number of times in rapid succession, the resulting contractions are of unequal height and are usually less in extent than the first contraction of the series. The extra contractions of such a series are quick and jerky, yielding a very irregular curve, like that illustrated by Fig. 6, *a*. If tetanic stimuli of appropriate strength be employed, the ventricle may either beat at a more rapid rate or be thrown into fibrillary contractions. Should the latter happen, the form of curve then resembles that of Fig. 6, *b* and *c*.

The reaction toward tetanic stimuli in the chloralized heart is very different. The muscle is more sluggish even in the early stages of the poisoning; the tendency of the ventricle to pass into fibrillary contractions, following successive stimuli of moderate strength, gradually disappears; and instead of tetanic stimuli resulting in a series of irregular contractions, as illustrated by Fig. 6, *a, b*, and *c* from the normal heart, the extra contractions are of more uniform height, see

Fig. 6, *d*. As the poisoning advances, the height of the extra contractions exceeds the height of the first contraction of the series, the number of stimuli required to maintain this height being very small. In still more advanced stages of the poisoning, when contractility has been greatly impaired, the so-called tetanus curve ascends rather than descends, see Fig. 6, *e, f, h*, and *i*. Rohde's¹ Figs. 1, *b*, 6, *b*, 7 and 9 are excellent, and show in addition to the illustrations given in this paper so-called tetanus curves in which the individual contractions have been more or less fused. Strips of terrapin heart treated with Ringer's solution plus an excess of calcium chloride also show summated contractions, a slightly shortened absolute refractory period, and a marked tendency to yield compound contractions resembling summation and incomplete tetanus, these being preceded by a decrease in the extent of the contraction. Strips treated with Ringer's solution saturated with ether show similar phenomena, but so-called summation and incomplete tetanus are less marked, and it is difficult to secure curves resembling complete tetanus until after considerable diminution of contractility.

Walther² observed that conditions which favor the production of so-called tetanus and summation of the frog's heart likewise favor the production of *treppe*. I also have noticed a marked tendency to *treppe* in the chloralized heart at the time that it is exhibiting the phenomena of summation and tetanus. Whatever may be the underlying conditions necessary to the production of each of these phenomena, it seems evident that they are closely related. For it is possible to conceive of the so-called tetanus curves as being composed of a series of individual contractions showing a distinct *treppe*, which is due either to a general improvement in the irritability of the heart-muscle or to an increased conductivity whereby the entire musculature is thrown into co-ordinated action instead of responding with more or less localized contractions.

It is important to bear in mind that these compound contractions are, as a rule, less in height than the normal contractions of the undrugged heart. Provided the poisoning is not carried too far, it can be shown that the muscle may be revived so that it will, by appropriate treatment, again yield contractions that are normal and higher than the compound contractions. If the normal contractility is regained, the muscle ceases to yield contractions which simulate sum-

¹ ROHDE: *Loc. cit.*, pp. 107, 112, 113.

² WALTHER: *Archiv für die gesammte Physiologie*, 1900, lxxviii, p. 597.

mation and tetanus. It is evident, therefore, that these compound contractions depend for their existence upon a condition of the muscle which produces reduced or partial contractions in response to single induction shocks. What the exact nature of the process may be, it is at present impossible to say. As was mentioned in discussing summation, however, the results closely resemble the condition produced by low temperatures.

That which is called tetanus and summation by Rohde may be explained as a phenomenon due, in the first place, to a retardation of the process of diastole; in the second place, to an improved conduction and irritability of the muscle following upon repeated stimulation. In any event, it must be recognized that this so-called tetanus of heart-muscle differs from that of skeletal muscle inasmuch as the chloralized heart continues to exhibit a definite refractory period extending over the greater part of the phase of the contraction.

SUMMARY.

1. The ventricular muscle of the frog or terrapin when dosed with chloralhydrate shows a gradual diminution in contractility. During the earlier stages of the poisoning the irritability increases, after which it gradually diminishes. The spontaneous beats become weaker and finally disappear. Eventually the muscle loses all irritability to the strongest induction shocks.

2. During the progressive stages of the poisoning the refractory period is at first somewhat shortened, so that the muscle becomes irritable to artificial stimulation toward the end of systole. There remains, however, a definite refractory period, designated in this paper as the shortened absolute refractory period, which extends over most of the systolic phase and is retained as long as the heart shows any response to artificial stimulation.

3. At a certain stage in the poisoning the heart-muscle when stimulated by two successive shocks exhibits the phenomenon of summated contractions and gives on repeated stimulation a curve resembling that of incomplete tetanus of skeletal muscle. In the later stages of poisoning this tetanic curve may show a gradual rise.

4. The maximum shortening reached by these so-called compound contractions is always less than that shown by the normal single contractions of the unpoisoned muscle.

5. Similar phenomena of summated contractions and compound contractions resembling tetanus may be obtained from heart-muscle

that is cooled to near zero centigrade, when treated with ether, or when treated with an excess of calcium. In all such cases the individual contractions are first diminished in extent before the phenomenon of summation is exhibited. The view is suggested that this summation may be due to an improved condition of conductivity brought on by successive stimuli whereby the entire musculature is brought into action.

6. The characteristic properties of the heart-muscle are not lost as a result of the action of chloralhydrate. A definite refractory period remains, and the all or none law holds true at the time when the heart shows the characteristic effects of the poisoning, such as complete loss of spontaneous beats and the appearance of the phenomenon of summated contractions.

RECORD IN DETAIL OF THREE EXPERIMENTS.

Experiment 77, April 3, 1906. — *Rana catesbiana* (very large ♀).

3.00–3.33 P.M. Pithed and fastened to cork sheet as described under head, "Method."

3.36. Rate of rhythm equals $28\frac{5}{8}$ beats per minute; height of contraction equals 8.7 mm.

4.3. Secondary coil 20 cm. from primary; no response to first nine stimuli; to tenth stimulus, response late in diastole; later response one-fourth length of diastole from tip of crescent.

4.18. Rate, $22\frac{1}{8}$ per minute; height, 10.7 mm.

4.21 $\frac{1}{2}$. Injected into anterior abdominal vein 3 c.c. of 0.75 per cent solution chloralhydrate (Eimer and Amend). Height of contraction is immediately decreased; systole lengthened; rate of rhythm slowed.

4.23–4.27. Distinct summation; S22 cm.¹ Absolute refractory period shortened (?); height, 8–8.8 mm.; rate, 10.9 per minute.

4.28 $\frac{1}{2}$. Rate, 13.6 per minute; height, 8 mm.; responds to S24 cm.

4.28 $\frac{1}{2}$ +. Ceases to respond to S24 cm., responds to S23 cm.

4.37. Rate, $19\frac{2}{7}$ per minute; S23 cm. no response, S22 cm. response late in D; S21 response one-third in D.

4.40. Height of contraction from artificial stimulus higher than that of spontaneous contraction.

4.45. Distinct treppe in response to successive artificial stimuli.

4.51. Responds to S23 cm., one-third in D.

4.54. Responds to S24 cm., one-third in D, distinct summation. Rate, $20\frac{5}{8}$ per minute; height, 7.2 mm.

5.00. Height, 7.6 mm.; responds to S24 cm., one-fifth in D.

¹ S22 cm. equals secondary coil 22 cm. from primary.

- 5.4. Rate, $21\frac{1}{2}$ per minute ; height, 7.9 mm. ; responds to S25 cm., one-fourth in D.
- 5.6. Rate, $21\frac{5}{11}$ per minute ; height, 8.1 mm. ; responds to S25 cm., one-fourth in D.
- 5.8. Rate, 22.5 per minute ; height, 8.1 mm.
- 5.11. Rate, $21\frac{2}{11}$ per minute ; height, 8.7 mm.
- 5.17. Rate, $21\frac{2}{11}$ per minute ; height, 11.5 mm.
- 5.40. Responds to S25 cm., very near beginning of D.
- 5.48. Responds to S29.5 cm., very near beginning of D.
- 5.49. Responds to S30 cm., but uncertain, not always calling forth an extra contraction.
- 5.53. Responds to S30 cm., but less certain than at 5.49.
- 5.57. Rate, 23.5 per minute ; height, 11.9 mm.
- 5.58. Injected 1 c.c.
- 5.59 $\frac{1}{2}$. Rate, 22.2 per minute ; height, 10.5 mm. ; responds to S30 cm.
- 6.5 $\frac{1}{2}$. Rate, 21.7 per minute ; height, 12 mm. ; responds to S29 cm., one-fourth in D.
- 6.15 $\frac{1}{2}$. Rate, $22\frac{1}{11}$ per minute ; height, 11.7 mm. ; ceased to respond to S29 cm.
- 6.18. Responds to S28 cm. in beginning of D.
- 6.21. Rate, 22.5 per minute ; height, 11.7 mm.
- 6.22. Injected 1 c.c.
- 6.25. Rate, $20\frac{7}{8}$ per minute ; height, 9.8 mm. ; responds to S28 cm. toward end of D ; summation marked ; latent period short.
- 6.28. Rate, $19\frac{3}{8}$ per minute ; height, 10.7 mm. ; responds to S29 cm. in beginning of D.
- 6.43. Rate, $20\frac{5}{8}$ per minute ; height, 10.7 mm. ; ceases to respond to S29 cm., but responds to S28 cm., one-fourth in D.
- 6.48. Injected 2 c.c.
- 6.50. Rate, 20 per minute ; height, 10.2 mm. ; responds to S28 cm. in beginning of D ; form of curve is changed, slow systole, rapid diastole.
- 6.55. Rate, $17\frac{5}{8}$ per minute ; height, 11.7 mm. ; responds to S28 cm., but not to S28.5 cm.
- 7.2. Ceases to respond to S27.5 cm.
- 7.13. Rate, 18 per minute ; height, 11.9 mm. ; responds to S27 cm., one-third in D
- 7.15. Injected 2 c.c.
- 7.17. Rate, $15\frac{3}{4}$ per minute ; height, 11.8 mm.
- 7.20. Rate, 15 per minute ; height, 12.2 mm ; responds to S27 cm., but not to S28 cm. ; compensatory pause lengthened.
- 7.31. Injected 1 c.c.
- 7.46. Responds to S24 cm., but not to S25 cm.

7.52. Preparation, in response to successive stimuli, yields a compound contraction resembling incomplete tetanus.

8.00. Injected 2 c.c.

8.1. In response to number of successive stimuli heart assumes a rhythm of $32\frac{1}{2}$ per minute; height, 8.9; changes to slower rhythm.

8.40. Rate, 3 per minute; height, 13.5 mm.; cardiogram more or less flat-topped.

8.44. Rate, 20 per minute.

8.44-9.43. Heart ceases to beat spontaneously; does not respond to S22 cm.; summation; excellent compound curve resembling tetanus.

10.30. Coil 22, 20, 18, 16, 14, 12, 10, 8, 6, 4, 2, 0, -15, all contractions same height; refractory period does not infringe upon the systole further than at 4.27.

April 26, 1906. — *Rana catesbiana*.

11.00 A.M. Frog pithed as described in "Method."

11.3. Rate, 32 per minute; height, 10.9 mm.

11.22. Rate, 27.5 per minute; height, 10.1 mm.

11.23. Injected 2 c.c.

11.23. Rate, 26.2; height, 7.6 to 5.4 mm.

11.24. Rate, 18; height, 4.9 to 6.5 mm.

11.24 $\frac{1}{2}$. Heart stops; does not respond to S19 cm.; but does to S18 cm.

11.25. In response to S17 cm. marked summation; absolute refractory period not shortened.

11.27 $\frac{1}{2}$. Response to S18 cm.; begins to beat spontaneously. Rate, 17.5 average height, 8.8.

11.29. Rate, 20.6; height, 9.1 mm. In response to S17 cm. A. R. P. slightly shortened.

11.38. Responds to S20 cm.

11.42. Rate, 25.5; height, 10.3; responds to S21 cm.

11.45 $\frac{1}{2}$. Rate, 26.2; height, 10 mm.

11.46. Injected 2 c.c.

11.48 $\frac{1}{2}$. Rate, 27.2; height, 10.1 mm.

11.50. Injected 2 c.c.

11.53. Injected 4 c.c.; rate, 9.5; height drops from 9.8 to 4.7, and later to 3.5 mm.

11.55 $\frac{1}{2}$. Rate, 15; height, 5 mm.; marked summation in response to S21 cm.

11.57. Muscle readily goes into so-called tetanus.

12.00 M. Responds to S23 cm., but not to S24 cm.

12.29 P.M. Rate, 20; height, 9 mm.

12.42. Injected 2 c.c.

- 12.42+. Rate, 3 per minute; height gradually decreased thus 9, 8.3, 4.2, 1.9, 0 mm.
- 12.44. Responds to S22 cm. Height, 1.4 mm.
- 12.45. Ceases to respond to S22 cm.
- 12.46½. Spontaneous contraction after long intervals of rest.
- 12.48. Height, 5.1 mm.; summation marked; A. R. P. normal.
- 12.53. Rate, 6 per minute; height, 3 mm.
- 1.3. Responds to S24 cm., but not to S25 cm.
- 1.5. Responds to S21 cm., but not to S22 cm.
- 1.7. Injected 1 c.c. Rate is slowed; height decreased; A. R. P. shortened as at 11.29; latent period lengthened.
- 1.30. Definite refractory period as at 1.07 in response to S16 cm.
- 1.32. Injected 1 c.c.; ceases to beat spontaneously; in response to S16 cm. contraction very weak.
- 2.15. Responds to S18 cm. but not to S19; definite refractory period; height, 0.5 mm.

Experiment 81, April, 1906.—*Rana catesbiana* (medium sized).

- 10.00 A.M. Frog pithed and fastened in place as described in method.
- 10.16. Rate, 50.4 per minute; height, 10.8 mm.; responds to S25 cm. one-third in D.
- 10.18. Rate, 52.5 per minute; height, 10.2 mm.; responds to S25 (uncertain).
- 10.24. Injected 2 to 4 c.c. In course of 20 seconds, height is decreased from 9.8 to 5 mm., then ceases to beat for 38 seconds, after which a single contraction is followed by a pause of 18 seconds. The heart now continues to beat for a time at a rate of 30 per minute; height, 3.3 mm.; slight increase in tone.
- 10.27. Rate slower, contractions very feeble.
- 10.31. Height, scarcely 0.5 mm.; refractory period still present even with S13 cm.; ceases to beat spontaneously.
- 10.38. Strong stimuli call forth weak contractions; refractory period still present.



William Henry Schultz was born at Canal Fulton, O., September 28, 1873. He received early training in the public schools of Doylestown, Navarre, and Marshallville, O. Before completing the work in the school at Marshallville, however, he accepted a clerkship, during which time, studies were continued at night. At the age of twenty-one, 1894, he entered Baldwin University, Berea, O., where in the year 1899 he was graduated with the Ph.B. degree. By special arrangement during the senior year, courses were pursued in Organic Chemistry, Histology, and Anatomy at Western Reserve University.

In the fall of 1899, Mr. Schultz was called to Shorter College, Rome, Ga., where he organized the Science Department. He continued to give instruction in this school until 1903, at which time he resigned in order to attend the Johns Hopkins University as a graduate student. In the fall of 1904, he accepted a position at the Southwestern Baptist University, Jackson, Tenn., where he reorganized the Science Department. One of the intervening summers had been spent at the University of Chicago (1900), studying mathematics, and one at the Marine Biological Laboratory (1901), studying Embryology. The summer of 1905 was also spent at the University of Chicago, doing work in Quantitative Analysis and Organic Chemistry. In the fall of 1905, he again entered the John Hopkins University. The same year, he was appointed Fellow in Physiology, and was reappointed for the year 1906-07.

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